Guidance on legislation

Clinical investigations of medical devices – guidance for pre-clinical assessors

November 2013

Medicines and Healthcare Products Regulatory Agency

Contents

This document replaces Guidance Note 4 ‘Pre-clinical assessment guidance for assessors’

Revision history

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V1.0	November 2013	n/a

The purpose of this document is to explain to expert assessors the background to and the system for the pre-clinical assessment of clinical investigations of medical devices, under the provisions of the UK Medical Devices Regulations implementing the Active Implantable Medical Devices Directive and the Medical Devices Directive.

1 The purpose of clinical investigations under the provisions of the directives

In order for a medical device to become freely available on the market within the EU, a CE-marking for the device must be obtained. In order to obtain this marking, a manufacturer must go through one or more conformity assessment procedures to confirm that the design and production of the device ensure compliance with all relevant essential requirements of the relevant directive.

In essence the essential requirements are intended to ensure that:

- devices do not compromise the clinical condition or safety of patients, users or, if appropriate, any third party
- devices achieve their intended purposes as designated by their manufacturers; and
- any risks associated with the use of a device are judged by informed clinical opinion to be acceptable when weighed against the benefits to the patient and compatible with a high level of protection of health and safety.

Ensuring compliance with these essential requirements, particularly for those devices associated with a higher risk, may require a review of clinical data. In many cases these data will be available from scientific literature or will be based on previous experience of the use of a device for a particular designated purpose. However, in certain circumstances involving, for example:

- the introduction of a completely new concept or type of device into clinical practice
- where an existing device is modified in such a way that it contains an entirely novel feature, or where the modification has an important physiological effect
- the use of a device, either CE-marked or non-CE-marked, is proposed for a new purpose or function
- the use of new materials previously untested in humans, coming into contact with the human body, where biocompatibility and biological safety will need to be considered

clinical data may only be available from a specifically designed clinical investigation and in these cases the manufacturer should carry out a clinical investigation before CE marking their device.

2 Role of the competent authority in relation to clinical investigations

In the UK, the competent authority for the purposes of the Medical Devices Directives is the Medicines & Healthcare Products Regulatory Agency (MHRA), an executive agency of the Department of Health.

Manufacturers are required by the Regulations to notify the MHRA of their intention to undertake a clinical investigation of a non-CE-marked medical device within the UK, at least 60 days before commencement of the proposed investigation and to submit the required documentation as set out in the Medical Devices Regulations.

At the end of the 60 day period following notification, the proposed clinical investigation may proceed unless the MHRA has notified the manufacturer within that period that, on grounds relating to health or safety, the device should not be made available for the purposes of that investigation (Medical Devices Regulations: Section 16(4)). However, provided the MHRA is satisfied that there are no grounds for objection, it may notify the manufacturer that the report on the proposed clinical investigation is favourable, before the 60 day time period has elapsed.

Circumstances in which the MHRA may object to an investigation proceeding include:

- where there are reasonable grounds to suspect that a device does not satisfy relevant essential requirements; or
- where there are reasonable grounds to suspect that the clinical investigation is not subject to controls equivalent to the requirements of the relevant European Standard (ISO14155); or
- where there exists professional opinion on the proposed clinical investigation which states that the risk benefit analysis given is inaccurate and that, were the investigation to take place, there would be a significant probability of serious illness, injury or death to the patient or user; or
- where insufficient information has been submitted to enable a proper assessment of the safety aspects of the proposed clinical investigation to be made; or
- where, because the manufacturer has delivered the documentation necessary for the assessment so late that insufficient time remains within the 60 day notification period for an assessment to be made which is adequate to determine whether the proposed clinical investigation involves any risk to health or safety.

The MHRA believes that the way to ensure that it can carry out its functions properly in relation to clinical investigation is:

- by setting out for manufacturers full details of the information which they must submit to or keep available for the MHRA under the provisions of the Medical Devices Regulations (a Guidance Document for Manufacturers covering both Directives has been prepared);
- by setting up a group of assessors who are experts in a number of areas relevant to a clinical investigation, and to whom the MHRA can apply for an opinion in relation to those aspects of the investigation; and
- by setting up an information handling timetable which is such as to enable the MHRA to carry out a satisfactory assessment within the 60 days allowed.

3 Role of the expert assessor

The expert assessor is requested by the MHRA to make an assessment of the relevant features of the proposed clinical investigation in the area of expertise in which he/she has been asked to give an opinion. This is in order that the MHRA can make an informed judgement as to whether there are grounds for objection to a clinical investigation proceeding on the basis of potential risk to the subject or user, or whether it is reasonable, based on the submitted information, to proceed to a clinical investigation in human subjects.

4 Required documentation

Two categories of documentation are required, namely:

- initial information which the manufacturer is required to submit as part of the application for assessment of a clinical investigation of a medical device (Medical Devices Regulations: 16(3) which incorporates Annex VIII, paragraph 2.2); and

- additional information which the manufacturer is required to hold and which may be requested by the assessor through the MHRA (Medical Devices Regulations 16(1)(b) which incorporates Annex VIII, paragraph 3.2).

Assessors are advised that the documentation coming within the second category should only be requested if essential in order to make a reasoned and adequate assessment.

The information falling within these two categories is set out in appendix 1 and appendix 2 of this document.

5 Submission to assessor and timetable for assessment

A timetable has been devised in order to provide the necessary time for adequate assessment of the submitted documentation within the time constraints laid down.

- The MHRA will, immediately following the submission of required documentation by the manufacturer, contact the relevant expert assessors to check availability for the purposes of making an assessment of the proposed clinical investigation. In exceptional circumstances, a review meeting of all assessors may be required to discuss an individual clinical investigation. Under these circumstances, suitable arrangements will be made, as necessary. The documentation will be sent to the agreed experts, and will specify the subject area in which each assessor is requested to carry out the assessment, e.g. clinical research, toxicology, sterilization, etc. Each expert is asked to consider only this area/these areas in making an assessment of the submission.

- Each expert is required to undertake the assessment of the information provided within the designated area of expertise, within two weeks of receipt of the documentation. It is envisaged that the assessment will take between 4-6 hours for each individual assessor in the majority of submissions. If no additional information is required, a report as to whether there are grounds for the MHRA to object to the commencement of the clinical investigation, should be provided.

- Any additional information required by the assessor must be requested through the MHRA within two weeks of receipt of the original documentation. The request will be assessed by the

MHRA to ensure that it is valid under the Directives (see Appendix 2 of this document). **At no stage may an assessor contact the manufacturer directly**. On receipt of the additional information the assessor is required to complete the assessment as quickly as possible and in any case within two weeks.

- Relevant forms for requesting additional information will be sent to each assessor with each submission.

- A timetable showing the date by which each significant phase of the assessment process should be completed will be sent to each assessor with each submission.

- Once the assessment has been completed, each assessor is required:
  (a) to complete and return the final report form which will have been sent with the original submission; and
  (b) to return all the documentation received from the MHRA.

- The names/addresses/phone numbers/fax numbers of other assessors involved with an individual submission may be obtained from the MHRA on request, in order to allow discussion between assessors if necessary. Such discussions should not involve any third party as all information supplied is classed as 'Restricted - Commercial'. The MHRA should be informed that such discussions have taken place by the assessor noting this in the final report form.

6 Confidentiality and conflicts of interest

All information submitted to an assessor must be treated as 'Restricted - Commercial'. Accordingly, assessors will be required to enter into a written agreement to protect the confidentiality of the information supplied to them in the course of an assessment. They will also be required to disclose in the agreement any potential or actual conflicts of interest which may have a bearing on any assessments.

The names of all assessors will be kept confidential and will not be revealed to the manufacturer.

7 Payment

A fixed fee will be paid to each external assessor for review of each submission. The fee will include payment to cover costs of returning documentation to the MHRA. An additional fee will be paid to cover travel costs if an expert assessor is required to attend a review meeting.

8 Documents

All documentation will be sent to each assessor by courier or registered mail.

On completion of the assessment, each expert assessor must return all the documentation by registered mail or courier.

Requests for further information should be sent by email to the designated MHRA contact for the given notification (contact details will be provided with the documentation).

9 Further information

Any problems or queries arising in connection with a pre-clinical assessment should be directed to:
Daniella Smolenska, European and Regulatory Affairs, Medicines & Healthcare Products Regulatory Agency Tel: 020 3080 7363
Email: daniella.smolenska@mhra.gsi.gov.uk or mb-mda-era@mhra.gsi.gov.uk

10 Glossary of terms

Active implantable medical device
means any active medical device which is intended to be totally or partially introduced, surgically or medically, into the human body or by medical intervention into a natural orifice, and which is intended to remain after the procedure.

Active medical device
means any medical device relying for its functioning on a source of electrical energy or any source of power other than that directly generated by the human body or gravity.

Adverse device event
means a device-related adverse event.

Adverse event
means any undesirable clinical occurrence in a subject whether it is considered to be device-related or not.

Clinical investigation
means any systematic investigation or study in human subjects, undertaken to verify the safety and performance of a device, under normal conditions of use.

Clinical investigation plan
means a document which includes detailed information on the rationale, aims and objectives, design and proposed analyses, methodology, and conduct of the clinical investigation.

Clinical investigator
means the person responsible for the conduct of a clinical investigation and who takes the responsibility for the health and safety of the subjects involved.

Device intended for clinical investigation

means, within the context of this document, any device intended for use by an appropriately qualified practitioner when conducting clinical investigations in an adequate clinical environment.

Implantable device
means any device which is intended to be totally introduced into the human body, or to replace an epithelial surface or the surface of the eye, by surgical intervention and which is intended to remain in place after the procedure. Any device intended to be partially introduced into the human body through surgical intervention and intended to remain in place after the procedure for at least thirty days is also considered an implantable device.

Invasive device
means a device which, in whole or in part, penetrates inside the body, either through a body orifice or through the surface of the body. A body orifice includes any natural opening in the body, as well as the external surface of the eyeball, or any permanent artificial opening such as a stoma.

Local research ethics committee
means an independent and properly constituted body of medical professionals and non-medical members whose responsibility is to ensure that the health, safety and human rights of the patients participating in a particular clinical investigation are protected.

Medical device
means any instrument, apparatus, appliance, material or other article, whether used alone or in combination together with any accessories or software necessary for its proper functioning, intended by the manufacturer to be used for human beings in:

- the diagnosis, prevention, monitoring, treatment or alleviation of disease or injury;
- the investigation, replacement or modification of the anatomy or of a physiological process;
- the control of conception;

and which does not achieve its principal intended action by pharmacological, chemical, immunological or metabolic means, but which may be assisted in its function by such means.

Multicentre investigation
means a clinical investigation, conducted according to a single clinical investigation plan, which takes place at different investigation sites.

Performance of device
means the action of a device with reference to its intended use when correctly applied to the appropriate subjects.

Principal clinical investigator
means a clinical investigator appointed by the manufacturer to co-ordinate the work in a multicentre clinical investigation or the work of several clinical investigators at one site.

Relevant essential requirements
means such of the essential requirements, or such aspects of the essential requirements as apply to a device, not including, in the case of a device intended for clinical investigation, such of those requirements, or aspects of them, as are the subject of the investigation.

Subject
means a human being, who is either a patient or a non-patient volunteer, participating in a clinical investigation.

Surgically invasive
means an invasive device which penetrates inside the body, other than through an established body orifice, with the aid or in the context of a surgical operation.

Appendix 1 – Documentation required for all clinical investigation submissions

The information listed below which is marked with a * forms part of the additional information which the manufacturer must undertake to keep available for the MHRA on request by virtue of Regulation 16(1)(b) of the Medical Devices Regulations which incorporates Annex VIII, paragraph 3.2. If they wish, manufacturers may submit any of this additional information at the time of their initial submissions, as doing so may help the MHRA to assess a submission within a shorter period of time.

General information required

- Date of submission
- Applicant's name/address/telephone number/fax number and contact name for communication
- Whether a first submission or a re-submission
- If re-submission with regard to the same device, previous date(s) and reference number(s) of earlier submission(s)
- *If other Member States are participating in the clinical investigation as part of a multi-centre/multinational study, details of applications to other Competent Authorities in the EU
- *Details of any approval by a notified body of manufacturing processes at the site(s) where the device is manufactured

Details allowing device to be identified

- Generic name of device
- Model name
- Model number(s), if any

Other device details

Identification of any novel or untested features

- *Summary of experience with any similar devices manufactured by the company making the device to be tested, including length of time on the market and a review of performance related customer complaints
- *Brief description of device and other devices designed to be used in combination with it
- *Brief description of device, including materials in contact with the body and identification of any pharmacological components or tissues of animal/human origin
- *A summary of the relevant or other Standards applied in full or in part, and, where Standards have not been applied, a description of the solutions adopted to satisfy the essential requirements specified in the Medical Devices Regulations as appropriate
- *Instructions for use

Clinical investigation plan

A copy of the Clinical Investigation Plan and the Investigator's Brochure must be provided, which should include the following information;

General information

- Name(s), qualifications, address(es) of clinical investigator(s), and principal clinical investigator for a multicentre clinical investigation
- Name(s), address(es) of the Institution(s) at which the clinical investigation will be conducted
- Description of intended purpose of device
- Aims and objectives of clinical investigation
- Analysis of potential risks and benefits and how foreseeable risks will be minimised
- Reference to important relevant scientific literature with a bibliography (if any)
- A copy of the Local Research Ethics Committee approval, whether complete or qualified

Design

- Number of devices to be used
- Duration of study with start and finish dates and proposed follow-up period
- Numbers of patients to be involved
- Whether control group is planned
- Criteria for subject selection, inclusion, exclusion, withdrawal
- What provisions, if any, have been made by the manufacturer for the recovery of the device (if applicable) and prevention of unauthorised use

Data collection / analysis / statistics

- Description of methods of subject follow-up and assessment during investigation
- Description of procedures to record and report severe adverse events and adverse device events
- Description and justification of statistical design, method and analytical procedures

Appendix 2 – Documentation to be kept available for the MHRA

The following should not be supplied with the initial submission but is available to assessors on request:

- Full description of device, including a list of accessories, principles of operation and block or flow diagrams of major components
- Principal design drawings and circuit diagrams, including materials and biomaterials, together with a description and explanations necessary for the understanding of the said drawings and diagrams
- Description of manufacturing methods
- Detailed description of how biocompatibility and biological safety have been addressed
- Details of the method(s) of sterilization
- Description of software, logic and constraints (if relevant)
- Pre-clinical experimental data including results of design calculations and of mechanical and electrical tests and reliability checks, and any performance tests in animals.